

Molecular pathology of colorectal carcinoma

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Colorectal carcinoma (CRC) develops as a result of progressive accumulation of genetic and epigenetic alterations that lead to neoplastic transformation of colorectal epithelium. Five overlapping molecular pathways of tumor initiation and progression are known for colorectal carcinogenesis: the chromosomal instability pathway (CIN), the microsatellite instability pathway with high levels of instability (MSI-H), the microsatellite instability pathway with low levels of instability (MSI-L), the hMYH pathway (MYH), and the CpG island methylation pathway/phenotype (CIMP).

The vast majority (approximately 80%) of colorectal carcinomas develop through the chromosomal instability pathway (CIN) in the conventional adenoma-adenocarcinoma sequence. The hallmark of these CRC is that progression involves structural chromosomal alterations that are reflected in altered total DNA content, cytogenetic aneuploidy, and numerous allelic losses and gains. These CRC usually have inactivation of the adenomatous polyposis coli (APC) gene on chromosome 5q as the initiating event. Familial adenomatous polyposis with germline APC mutation is the inherited form of CRC in this pathway. Point mutations of the K-ras proto-oncogene and the p53 gene are frequent in CIN CRC.

CRC with high levels of microsatellite instability (MSI-H) comprise about 15% of cases. CRC in this pathway are characterized at the molecular level by numerous nucleotide substitutions and insertion/deletion mutations in repeated nucleotide sequences (microsatellites), MSI-H CRC result from inactivation of both alleles of a nucleotide mismatch repair, usually hMSH2 or hMLH1. These tumors usually have normal total DNA content, relatively normal cytogenetic karyotype, and infrequent allelic imbalances. Germline mutation of a mismatch repair gene causes hereditary non-polyposis colorectal cancer syndrome (Lynch syndrome), while most sporadic MSI-H CRC result from transcriptional silencing of the hMLH1 mismatch repair gene by promoter methylation, as described below. MSI-H CRC have distinctive clinical-pathologic features. These include right-sided location, poor differentiation, unusual histologic types (mucinous, medullary and signet-ring cell histology), absence of "dirty" necrosis, expansile growth pattern, numerous tumor-infiltrating lymphocytes, and prominent peri-tumoral lymphoid nodules, term Crohn's-like lymphoid response. Serrated adenomas may be an important precursor to MSI-H CRC.

CRC with low levels of microsatellite instability (MSI-L) are heterogeneous. The molecular mechanisms responsible for this small subset of

tumors is poorly understood, and the clinical-pathologic characteristics are not yet well defined.

CRC in the hMYH pathway have been described only recently. These infrequent CRC have mutations in both copies of the hMYH base excision repair gene due to inheritance of one mutated gene from each parent, resulting in bi-allelic alterations. Progression of these tumors is characterized by high frequency of G-to-T transversion mutations and by allelic loss on chromosome 18q, but the tumors have neither chromosomal instability nor microsatellite instability. Understanding of CRC in this pathway is in evolution.

About a third of CRC develop in the CpG island methylation pathway/phenotype (CIMP). CpG islands are 0.5 to 2 kilobase regions rich in cytosine-guanosine dinucleotide repeats that are present in the 5' region of approximately half of all human genes. Methylation of cytosine residues within CpG islands of promoter regions and proximal exons is associated with loss of gene expression by repression of transcription. This epigenetic mechanism is observed in physiologic conditions such as X chromosome inactivation and aging, as well as in neoplasia. In CRC with CIMP, transcriptional activation by methylation often occurs in numerous genes that are not usually unmethylated in non-neoplastic colorectal mucosa. Methylation is often concordant among numerous genes, and this concordant methylation defines the CpG island methylation phenotype (CIMP). Because of methylation of hMLH1, many CRC that develop due to CIMP also have MSI-H, whereas CRC with extensive methylation that does not involve hMLH1 have chromosomal instability. Clinical-pathologic features of MSI-H/CIMP tumors are similar to those in the MSI-H pathway, as described above. Microsatellite-stable CRC with CIMP also have characteristic clinical-pathologic findings included right-sided location, poor differentiation, and cribriform gland architecture, whereas corkscrew/serrated gland architecture is not seen in this molecular subtype.

The characteristics of the various molecular subtypes of CRC have impact on diagnosis, prognosis, and response and resistance to therapies. The best established association is that of MSI-H with hereditary non-polyposis colorectal cancer syndrome. About 95% or more of HNPCC carcinomas have MSI-H, and evaluation for MSI can contribute to diagnosis of the syndrome. Immunohistochemical characterization of the responsible abnormal mismatch repair gene can direct germline sequencing. In addition, stage-specific prognosis is improved in patients with MSI-H colorectal carcinoma in HNPCC and the sporadic setting. Allelic losses in CRC with chromosomal instability have been associated with poorer survival and with poorer outcome after fluoropyrimidine-based chemotherapy than microsatellite-stable carcinomas that lack allelic losses. CRC with CpG island methylation phenotype have also been reported to have adverse prognosis and poor response to chemotherapy.

In conclusion, the major molecular pathways leading to CRC have been identified. Some of the molecular characteristics are now used for clinical decision-making and patient management. Applications of molecular diagnostics based on the molecular pathways producing CRC are expected to expand as research results continue to evolve.